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Systemic sclerosis associated pulmonary hypertension: improved survival in the current era

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Objectives: To measure survival, haemodynamic function and functional class in patients with systemic sclerosis associated pulmonary arterial hypertension (SSc-PAH) in two treatment eras.

Methods: Six year longitudinal study of 92 consecutive patients with SSc-PAH diagnosed by cardiac catheterisation. Data were collected both prospectively and retrospectively. Patients were given basic treatment (diuretics, digoxin, oxygen and warfarin). Where clinically indicated, a prostanoid was used as advanced treatment (historical control group). From 2002, the range of treatments available expanded to include bosentan, which was generally the preferred treatment (current treatment era group). Survival was measured from the date of diagnosis of pulmonary hypertension by cardiac catheterisation. Six minute walking distance and haemodynamic function were measured at the time of diagnosis and at least one month after treatment was started.

Results: The historical control group comprised 47 patients, all of whom received basic treatment; 27 of these were also treated with prostanoids. The current treatment era group comprised 45 patients, all of whom received bosentan as preferred treatment. Kaplan–Meier survival in the historical control group was 68% at one year and 47% at two years. Survival in the current treatment era group was 81% and 71% ($p = 0.016$) at one and two years, respectively. Pulmonary vascular resistance increased in the historical control group (by 147 dyn·s·cm^{-5}), whereas in the current treatment era group, it remained stable over an average of nine months (decrease of 16 dyn·s·cm^{-5}, $p < 0.006$).

Conclusion: Survival of selected patients with SSc-PAH has improved in the current treatment era. In contrast to patients treated historically with basic drugs and prostanoids, patients treated in the current treatment era had improved survival associated with a lack of deterioration in cardiac haemodynamic function.

Patients with systemic sclerosis associated pulmonary arterial hypertension (SSc-PAH) in World Health Organization (WHO) functional class III or IV have a very poor prognosis; survival in the first year after diagnosis has been estimated at around 55%.[1 2] Death is usually caused by right heart failure as a result of increased pulmonary vascular resistance (PVR), the cause of which is unclear.[3] Basic medical treatment consists of diuretics, digoxin, anticoagulation and oxygen. Intravenous prostanoids, potent systemic and pulmonary vasodilators, improve haemodynamic function and functional class in patients with idiopathic pulmonary arterial hypertension and SSc-PAH.[3–5] Survival of patients with idiopathic pulmonary arterial hypertension has improved but this has not been shown in patients with SSc-PAH.[5–7]

In recent years, the drugs available for the treatment of SSc-PAH have expanded to include inhaled and subcutaneous prostanoids and now the endothelin-1 antagonists. In the UK funding for these drugs has become more readily available and we are now using these drugs in higher doses and in combination.

The prostanoids use cyclic AMP as a second messenger promoting pulmonary vascular dilatation and inhibiting smooth muscle proliferation, making them candidates for the treatment of pulmonary arterial hypertension.[8]

Endothelin-1, a 21 amino acid peptide, is a potent endogenous vasoconstrictor thought to play an important part in the pathogenesis of pulmonary hypertension.[9] Endothelin-1 is a potent mitogen affecting smooth cells and fibroblasts and is associated with inflammatory processes.[10–12] Endothelin binding sites have been found in association with fibrosis in the skin, lung and kidneys.[12 13] Endothelin-1 has also been found to be raised in patients with systemic sclerosis.[14 15] Bosentan, a non-peptide antagonist blocking both endothelin A and B receptors, which mediate the biological effects of endothelin-1, has recently been licensed for the oral treatment of pulmonary arterial hypertension in patients in WHO functional class III.

There is little information on the long term effects of advanced treatments on survival, functional class and haemodynamic measurements in patients with SSc-PAH. In this longitudinal study, we present the survival, haemodynamic changes, functional capacity and symptoms in patients with SSc-PAH in two cohorts of patients. The first group were treated with basic drugs and prostanoids. The second group were given basic drugs and a modern treatment approach.

METHODS

Setting

We studied patients with systemic sclerosis who were referred to the national pulmonary hypertension unit at the Royal Free Hospital, London specialising in connective tissue disease associated pulmonary arterial hypertension. Before 2002 only prostanoids (as advanced treatment) were

Abbreviations: BREATHE-1, bosentan: randomized trial of endothelin receptor antagonist therapy for pulmonary hypertension; CI, confidence interval; HR, hazard ratio; mPAP, mean pulmonary artery pressure; SSc-PAH, systemic sclerosis associated pulmonary arterial hypertension; SMWT, six minute walk test; WHO, World Health Organization

available to treat these patients, but funding for this therapeutic intervention was difficult to obtain. Since 2002 the range of treatments available has widened and patients' acceptance of these treatments has increased.

Patient selection

All patients fulfilled the American College of Rheumatology preliminary classification for systemic sclerosis.[16] Between 1998 and 2004, 185 patients with SSc-PAH were being followed up. Patients were included in or excluded from the study on the basis of the following criteria.

Inclusion criteria

We used the criteria applied to trials with inhaled iloprost, subcutaneous treprostinil and bosentan to select patients for treatment with bosentan as the preferred treatment in the current treatment era.[17–20] In these trials exercise capacity of 150–450 m and total lung capacity of $> 70\%$ were used. These correlated with the mid-range of our patient population. Patients in WHO classes I or II and with severe fibrosis or end stage disease were not enrolled. In an attempt to have matched cohorts, we used the same criteria retrospectively to select patients for the historical control group from the total SSc-PAH population. Therefore, the groups were equally matched concerning disease severity.

Inclusion criteria were: (1) pulmonary hypertension resting mean pulmonary artery pressure (mPAP) > 25 mm Hg, pulmonary capillary wedge pressure < 15 mm Hg and PVR > 240 dyn s cm^{-5}; (2) WHO functional class III or IV established with the patient treated conventionally; and (3) six minute walk test (SMWT) distance of < 450 m.

Exclusion criteria

Patients were excluded from both the historical control and current treatment era groups for one or more of the following criteria: (1) WHO functional class I or II, as there had been no trial evidence of benefit of treatment in this group; (2) interstitial pulmonary fibrosis resulting in total lung capacity of $< 60\%$ and either mPAP < 35 mm Hg or oxygen saturations at rest on air of $< 85\%$, or both, as excluded from other pulmonary hypertension treatment trials; and (3) cardiac index < 2.1 l/min/m^2, right atrial pressure > 11 mm Hg and mixed venous oxygen saturation $< 63\%$, substituted for SMWT < 150 m (used in other trials). We found that the SMWT was affected by the musculoskeletal element of the patient's associated connective tissue disease rather than by the severity of their pulmonary hypertension.

Basic treatment

Both the historical control group and the current treatment era group received basic treatment. This comprised diuretics (loop diuretics and spironolactone), digoxin, oxygen (at least 16 hours in every 24 hour period) if resting oxygen saturation was $< 90\%$ and warfarin. Calcium channel blockers (nifedipine, diltiazem and amlodipine) prescribed for Raynaud's phenomenon were continued. High dose calcium channel blockers were rarely used and withdrawn within six months because of lack of effectiveness.

Table 1 Dose of prostanoids used

Prostanoid	Dose*
Inhaled iloprost	10 μg/inhalation 6–9 times/day up to 20 μg/inhalation 6–9 times/day
Treprostinil	2.5–50 ng/kg/min
Intravenous iloprost	2–16 mg/kg/min
Intravenous epoprostenol	2–40 ng/kg/min

*Increased as tolerated.

Advanced treatment

Patients received advanced treatment with either prostanoids or bosentan according to best practice at the time (table 1). Before 2002, patients meeting criteria for advanced treatment received prostanoids (historical control group). Intravenous iloprost has been the prostanoid of choice during both eras, as it requires only once daily administration, and in our population with reduced digital dexterity, this was thought useful for compliance and reduction of infection. In the current era bosentan was the preferred treatment (current treatment era group). For the analysis, we used an intention to treat method. Patients treated as part of the historical control group with a prostanoid remained in this group even if they subsequently were treated with a newer approach. Intravenous prostanoids were added to or substituted for preferred treatment when clinically indicated—for example, if the patient deteriorated or could not tolerate the preferred treatment.

Historical control group

Advanced treatment consisted predominantly of intravenous iloprost (Ilomedin; Schering) or intravenous epoprostenol (Flolan; GlaxoSmithKline), and a few patients included in this study received inhaled iloprost (Ilomedin) or a subcutaneous prostacyclin analogue (treprostinil (UT15); Myogen). The choice of prostanoid and its mode of administration were determined for clinical and logistic reasons by both the supervising clinician (JGC) and the patient's preference. The mode of administration and the dosage of prostanoids were continually reviewed and were changed for clinical reasons or if patients developed adverse effects. For example, patients who developed leg cramps with intravenous iloprost were switched to epoprostenol and patients who deteriorated when taking inhaled iloprost may have been switched to intravenous iloprost.

Current treatment era

Patients received a starting dose of bosentan 62.5 mg twice daily and this was increased and maintained at 125 mg twice daily after four weeks. Liver aminotransferases were routinely checked in patients treated with bosentan because of its known adverse effects on hepatocellular enzymes.

Patients deteriorating despite preferred treatment started prostanoids either in combination with preferred treatment or on their own. Prostanoid doses were subsequently escalated as tolerated by the patients.

Patients were reviewed at least every three months in the pulmonary hypertension unit. No patients were lost to follow up. The vital status of all patients was confirmed in August 2004.

WHO functional class

WHO functional class and haemodynamic data were collected at baseline, before treatment was started and at six months.

Six minute walk test

Patients performed the SMWT in accordance with the American Thoracic Society guidelines.[21] Patients who were unable to perform the test were recorded as achieving a distance of 0 m. In the current treatment era group SMWT distances were measured at the start of treatment and after three months, six months and one year. SMWT distance data were collected retrospectively for the majority of the patients in the historical control group. Data were not available for some patients treated before 2002 when the government sponsored National Specialty Commissioning Group database was initiated.

Right heart catheterisation

Right heart catheterisation was performed in accordance with our previous reported protocol.[22] Follow-up right heart catheterisations were performed to assess the response to treatment and for clinical indications in patients who deteriorated. Our clinical practice was to perform follow-up right heart catheterisation three to six months after advanced treatment was started and thereafter annually. Only the haemodynamic data collected by the preset time intervals were included for analysis. Follow-up cardiac catheterisation in both groups was not performed for the following reasons: death (17), severe morbidity (4), severe right heart failure (2), patient refusal (6) and non-clinical reasons within the one year time interval (5).

Statistical methods

Patients were followed up from the date of diagnosis of SSc-PAH. This date was defined as the baseline date. Follow up ended on death or on 2 August 2004, whichever occurred earlier.

We examined changes in survival between the historical control group and the current treatment era group of patients by Kaplan–Meier methods. We then investigated the factors associated with increased survival by using Cox proportional hazards regression models.[23] The potential explanatory factors that were investigated were use of bosentan, presence of diffuse or limited scleroderma, sex, mPAP, PVR, age, calendar year of diagnosis and presence of pulmonary fibrosis. Factors that were significant at $p < 0.05$ in a single variable analysis were included in a multivariable analysis. We analysed the percentage changes in PVR, mPAP and cardiac index before and after advanced treatment was started in the two groups by the two-sample t test.

Lastly, we carried out a sensitivity analysis investigating overall survival in these patients. We fitted a Cox proportional hazards regression model to investigate factors associated with overall survival. We considered the use of bosentan to be a time updated covariate rather than a binary (yes/no) covariate.

Table 2 Baseline demographic data of historical control and bosentan treated groups of patients with systemic sclerosis associated pulmonary arterial hypertension

	Current treatment era (n = 45)	Historical controls (n = 47)	p Value
Mean age (years)	60 (11.3)	58 (11.1)	NS
Sex (men/women)	7/38	7/40	NS
Time from diagnosis to start of bosentan or prostanoid (days)*	36 (0–512)	72 (0–506)	<0.0001
SMWT distance (m)	207 (0–538)	179 (0–471)†	0.1
mRAP (mm Hg)	8 (6.1)	7 (4.4)	NS
mPAP (mm Hg)	40 (11.8)	40 (11.4)	NS
MAP (mm Hg)	102 (18)	95 (15)	NS
PVR (dyn·s·cm^{-5})	613 (345)	597 (359)	NS
Cardiac index (l/min/m^2)	2.6 (0.7)	2.7 (0.9)	NS
WHO functional class			
III	26 (58%)	36 (77%)	0.054
IV	19 (42%)	11 (23%)	
Scleroderma subset (%)			
Limited	43 (96%)	34 (72%)	0.0026
Diffuse	2 (4%)	13 (28%)	
Patients with pulmonary fibrosis	14 (31%)	22 (46%)	NS

Data are presented as the number (percentage) of patients, mean (SD) or median (range).
Comparisons were by χ^2 test, two sample t test and Mann–Whitney U test as appropriate.
*This includes 27 patients in the historical control group, as not all patients in this group started prostanoids; †data available on only 30 patients, a significantly higher proportion of whom were in class IV.
MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; NS, not significant at p<0.1; SMWT, six minute walk test; WHO, World Health Organization.

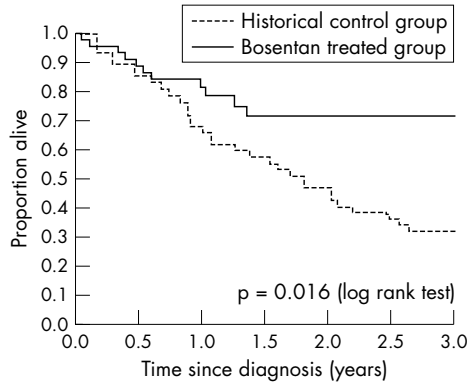

Figure 1 Kaplan–Meier analysis showing mortality among patients with systemic sclerosis associated pulmonary arterial hypertension (SSc-PAH). Historical group: one year survival 68%, two year survival 47%; current treatment era group: one year survival 81%, two year survival 71%.

RESULTS

From a total population of 185 patients with SSc-PAH diagnosed from 1998 to 2004, 93 patients were excluded from this study. The reasons for exclusion are listed below:

- WHO functional class I or II (n = 38): 22 patients from the historical treatment era and 16 patients from the current treatment era.
- Significant interstitial pulmonary fibrosis (n = 18): 10 patients from the historical treatment era and eight from the current treatment era.
- Higenbottam criteria for starting intravenous prostanoid and significant haemodynamic compromise (n = 37): 22 patients from the historical treatment era and 15 patients from the current treatment era.

After applying our inclusion and exclusion criteria we further analysed 92 patients in this study. There were 47 patients in the historical treatment era and 45 in the current treatment era. The groups did not differ significantly in terms of age, sex or baseline cardiopulmonary haemodynamic function. Table 2 shows baseline demographic data with comparisons between the current treatment era group and the historical control group.

Survival

Kaplan–Meier analysis showed one and two year survival rates of 81% and 71%, respectively, in the current treatment era and 68% and 47% in the historical group (fig 1) (p = 0.016, log rank test).

Table 3 shows the results of the Cox proportional hazard regression models investigating the factors associated with survival. Univariable analysis showed that higher baseline mPAP, higher baseline PVR, being in WHO class IV and being in the historical control group were associated with a decreased survival. Bosentan as the preferred treatment reduced the risk of death by 54% (hazard ratio (HR) 0.46, 95% confidence interval (CI) 0.23 to 0.92, p = 0.028). The risk of death increased by 11% for every 10 mm Hg increase in mPAP (HR 1.46, 95% CI 1.13 to 1.888, p = 0.0038). The risk of death increased by 15% for every 100 dyn·s·cm^{-5} increase in PVR at the time of diagnosis (HR 1.15, 95% CI 0.64 to 2.07, p = 0.0075). Patients in WHO class III at baseline had a 48% reduction in their risk of dying compared

Table 3 Results of Cox proportional hazards regression models investigating factors associated with overall survival

		Single variable analysis			Multivariable analysis		
Factor	**Variable**	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Treatment group	Current treatment era	0.46	0.23 to 0.92	0.028	0.40	0.19 to 0.84	0.016
	Historical control	1.00			1.00		
Baseline mPAP (mm Hg)	Per 10 mm Hg higher	1.46	1.13 to 1.88	0.0038	1.21	0.71 to 2.07	0.48
Baseline PVR (dyn·s·cm^{-5})	Per 100 dyn·s·cm^{-5} increase	1.11	1.03 to 1.20	0.0075	1.04	0.89 to 1.21	0.63
WHO class	III	0.52	0.29 to 0.96	0.036	0.64	0.32 to 1.27	0.20
	IV	1.00			1.00		

HR, hazard ratio; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance.

with those in class IV at baseline (HR 0.52, 95% CI 0.29 to 0.96, p = 0.036).

In a multivariable analysis of all variables, only the era of treatment was associated with improved survival and was associated with a 60% reduction in the risk of dying (HR 0.40, 95% CI 0.19 to 0.84, p = 0.016).

Six minute walk test

SMWT data were available for analysis for only 30 (64%) of the 47 patients in the historical control group (16 of the 17 for whom data were not available were in class III) but for all the patients (45; 100%) in the current treatment era group. To investigate whether the baseline SMWT distance was associated with survival, we analysed a subgroup of 75 patients (45 current treatment era patients and 30 historical control patients) who had measurements at baseline. Univariable analysis showed a significant association between SMWT distance and survival. In both groups, survival increased by 24% for every 100 m further a patient could walk (HR 0.76, 95% CI 0.58 to 0.98, p = 0.037). This effect, however, was not significant in a multivariable analysis (HR 0.81, 95% CI 0.59 to 1.12, p = 0.20).

Survival in subgroups

The presence or absence of mild pulmonary fibrosis (HR 1.15, 95% CI 0.64 to 2.07, p = 0.64) and type of scleroderma, whether diffuse or limited (HR 1.04, 95% CI 0.50 to 2.17, p = 0.91), had no significant impact on survival.

Changes in haemodynamic function

Haemodynamic data were available for 28 patients in the current treatment era group at both baseline and during follow up at a median (range) of 350 (41–1007) days after the first catheterisation and for 32 patients in the historical control group at a median of 225 days (79–896) after the first catheterisation (table 4). PVR did not change significantly in the bosentan treated group but increased in the historical control group. There was a significant difference in the mean percentage change in PVR of −1.4% (95% CI −1.3% to 10%) in the current treatment era group compared with a mean change of 38% (95% CI 13% to 63%) in the historical control group (p = 0.0058).

WHO class changes

Current treatment era group

Of the 26 patients who were in WHO class III at the time of starting treatment, after six months of treatment, 2 patients had died, 12 patients were in WHO class II, 9 patients were in class III and 3 patients were in class IV. Of the 19 patients who were in WHO class IV at the time of starting treatment, after six months of treatment, 4 patients had died, 1 patient was in class II, 8 patients were in class III, and 6 patients were in class IV (fig 2).

Historical control group

Of the 36 patients who were in WHO class III at the time of diagnosis, at six months 3 patients had died, 5 patients were in class II, 22 patients were in class III and 6 patients were in class IV. Of the 11 patients who were in WHO class IV at the time of diagnosis, after six months 3 patients had died, no patients were in class II, 2 patients were in class III and 6 patients were in class IV.

Time intervals between diagnosis and starting advanced treatments

Patients started taking either a prostanoid or bosentan only after the diagnosis of SSc-PAH was confirmed by cardiac catheterisation. For the 27 patients in the historical control group who were selected to start prostanoid at the time of diagnosis, the median delay in starting treatment was 72 days (range 0–512 days). The median delay during the current treatment era group in starting bosentan was 36 days

Table 4 Changes in haemodynamic function from baseline to follow-up cardiac catheterisation in historical controls and bosentan treated patients

		Current treatment era		Historical control		
Factor	**Variable**	**Mean**	**95% CI**	**Mean**	**95% CI**	**p Value***
mRAP (mm Hg)	Value at baseline	7.73	5.75 to 8.34	7.04	5.91 to 9.55	
	Absolute change at follow-up	1.50	−0.50, to 3.50	0.16	−1.58 to 4.81	
	% change at follow-up	89%	−7.2% to 184%	45%	−54.3% to 136%	0.51
mPAP (mm Hg)	Value at baseline	40.00	36.53 to 43.48	40.11	36.81 to 43.41	
	Absolute change at follow-up	1.08	−2.05 to 4.20	1.44	−1.54 to 4.41	
	% change at follow-up	3.3%	−5.3% to 12%	6.1%	−2.26% to 14%	0.64
PVR (dyn·s·cm^{-5})	Value at baseline	612.95	508.22 to 717.68	597.31	486.39 to 702.23	
	Absolute change at follow-up	−15.74	−96.10 to 64.62	147.34	5.47 to 289. 22	
	% change at follow-up	−1.4%	−13% to 10%	38%	13% to 63%	0.0058
Cardiac index (l/min/m^2)	Value at baseline	2.60	2.40 to 2.81	2.73	2.47 to 2.99	
	Absolute change at follow-up	0.044	−0.19 to 0.28	−0.22	−0.50 to 0.06	
	% change at follow-up	3.7%	−5.1% to 13%	−5.2%	−15.2% to 4.7%	0.17

*p Values calculated two-sample t test.
mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

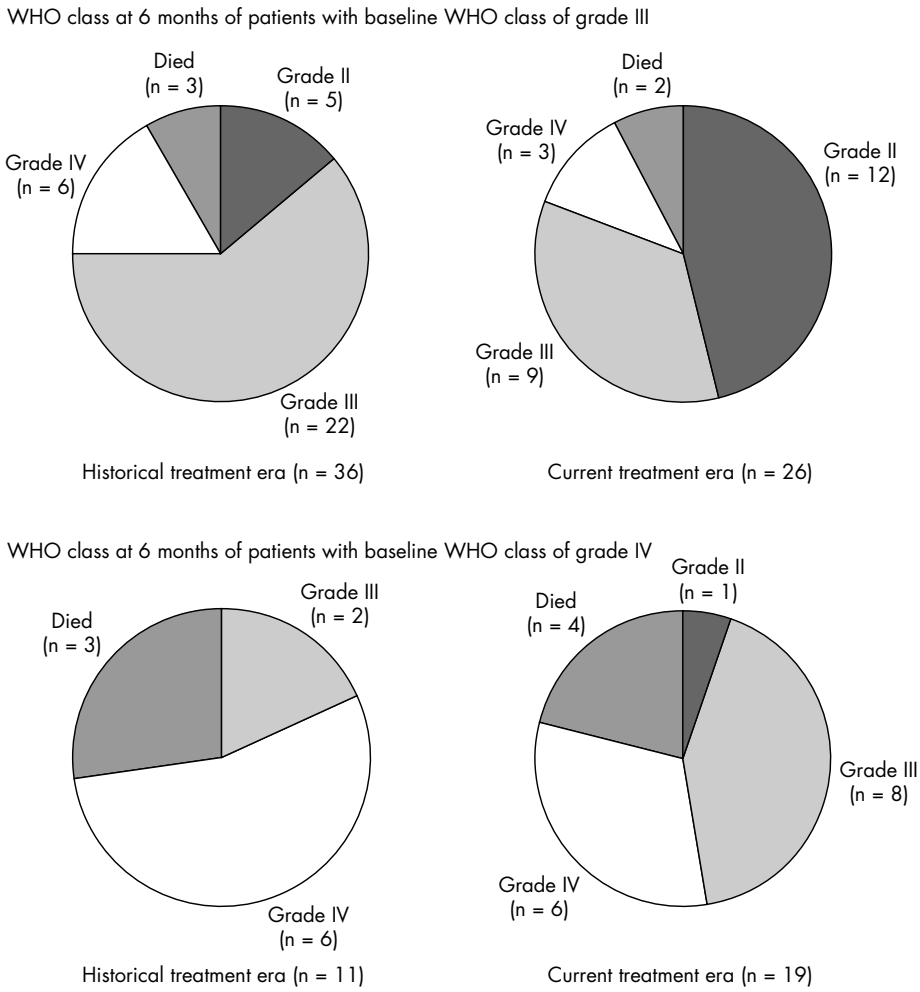

Figure 2 Change in World Health Organization (WHO) class from baseline to six months in patients in class III (top) and class IV (bottom) at baseline.

(range 0–506 days). The principle reason for the delay in starting either advanced treatment was securing agreement from the patients' National Health Service funding authorities that the treatment could be started.

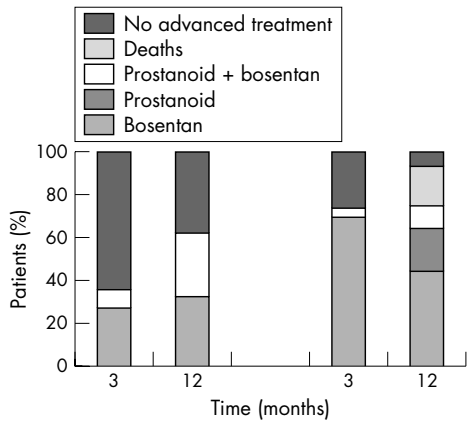

Figure 3 Graph showing type of advanced treatment and number of deaths among patients in the historical control group (HCG) and the current treatment era group (CTE) at three months and one year after diagnosis of pulmonary arterial hypertension.

Use of bosentan in historical control group

Two (4%) patients from the historical control group were treated with bosentan (fig 3): the first, at the patient's request, and the second due to recurrent Hickman line infection. The second patient later started iloprost because of clinical deterioration. The addition of bosentan was considered for a further four patients but this was not possible because of the failure to obtain health authority funding.

Use of prostanoids in the current treatment era group

Fourteen (31%) patients initially treated with bosentan were switched to prostanoid because of clinical deterioration (fig 3). Five of these patients remained on bosentan in combination with iloprost because of clinical deterioration when attempts were made to withdraw bosentan. These patients' median time to starting prostanoid was 204 days (range 89–726 days). Six (13%) patients discontinued bosentan because of abnormal liver aminotransferases, all of whom were subsequently treated with inhaled iloprost. These patients' median time to discontinuing bosentan was 149 days (range 43–267 days).

DISCUSSION

This is the first study to show an improved survival in a group of patients with SSc-PAH. PVR increased significantly in the historical control group but not in the current treatment era group. These data suggest that modern treatment improves survival probably by modifying the disease process and cardiopulmonary haemodynamic function.

We studied two cohorts of patients, all of whom had the same underlying pathophysiological process, similarly severe functional disability and similar baseline characteristics in terms of age, sex and cardiopulmonary haemodynamic function. More patients in the historical control group (36 patients; 76.6%) than in the current treatment era group (26 patients; 57.8%; $p = 0.054$) were in WHO class III. Although this was not significant, it may be considered to favour survival of those patients from the historical treatment era. The study population was therefore a high risk, homogeneous group with similar disease severity. We used modified BREATHE-1 (bosentan: randomized trial of endothelin receptor antagonist therapy for pulmonary hypertension) criteria to select patients in both the historical control and the current treatment era to have groups comparable regarding functional class (symptoms), haemodynamic function and exercise capacity (SMWT). The BREATHE-1 study excluded patients with an SMWT distance of < 150 m. We had noted a poor correlation between SMWT and haemodynamic function in patients with musculoskeletal disease (SSc) and believed that a haemodynamic threshold for automatic intravenous treatment was more appropriate for our population.

Starting advanced treatments was significantly delayed in the historical control group compared with the current treatment era group ($p < 0.0001$) and this may have contributed to the improved survival of those patients treated more recently. Survival is probably improved by the timely introduction of advanced treatments.

There is little information concerning survival of patients with SSc-PAH because they have constituted only a small proportion of the study populations in previous studies.[17 18] This is important when investigating survival and the possible influences of evolving treatments because the pathophysiological processes and survival may differ between the different types of pulmonary hypertension.[24–26]

Survival in the historical treatment era (or era before endothelin-1 antagonists)

Koh *et al*[27] reported a median survival of 12 months in 17 patients with SSc-PAH, and Kawut *et al*[2] reported a one year survival of 55% in 22 patients with SSc-PAH. In a large cohort of patients with SSc-PAH we have previously observed survival rates of 81%, 63% and 56% at one, two and three years, respectively, between 1998 and 2002 in patients with SSc-PAH in all functional classes.[22] However, these patients were at both ends of the risk spectrum and had generally lower mean pulmonary arterial pressures. Those patients at low and very high risk have been excluded from the current study. Those at low risk did not receive any treatment. Comparing survival between these two studies is therefore difficult.

Survival with prostanoids

Intravenous prostanoids have been shown to improve long term survival of patients with idiopathic pulmonary arterial hypertension as compared with historical controls from the National Institutes of Health registry.[27] No such control group has been available for the SSc-PAH population. No improvement in survival with prostanoid treatment has been reported, however, for the SSc-PAH population in data published to date.[2 5 28]

Treprostinil and survival

Some of the patients in the historical control group were treated with treprostinil, a prostacyclin analogue given subcutaneously. This has been shown to improve exercise capacity, signs and symptoms of pulmonary arterial hypertension and haemodynamic function in patients with SSc-PAH.[19] The greatest benefit from treprostinil was seen in those patients who could tolerate the highest doses but infusion site pain prevented dose increases in a large proportion of patients. The long term effect of treprostinil in patients with SSc-PAH remains to be established.

Inhaled iloprost and survival

Inhaled iloprost, a stable analogue of prostacyclin, has been shown to improve WHO functional class, exercise capacity and cardiopulmonary haemodynamic function in a small cohort of 35 patients with connective tissue disease associated pulmonary arterial hypertension but to a smaller extent to that seen in patients with idiopathic pulmonary arterial hypertension.[20] The long term effects of inhaled iloprost in SSc-PAH are unknown and no effects on survival have been documented.

Survival in the current era

Impact of bosentan in SSc-PAH

In a 12 week double blind placebo controlled pilot study of patients with pulmonary arterial hypertension (including five patients with SSc-PAH), bosentan was shown to improve exercise capacity and haemodynamic function.[18] Improvements were similar in a subsequent randomised controlled study including 47 patients with SSc-PAH in WHO functional class III or IV in which patients received bosentan or placebo.[16] There was a 3 m improvement in the bosentan group compared with a 40 m decline in the placebo group. WHO functional class, time to clinical worsening and cardiopulmonary haemodynamic function also improved. These improvements were less notable than those seen in the idiopathic pulmonary arterial hypertension population.

Impact of advanced treatment on WHO functional class

There was an overall improvement in WHO functional class in the current treatment era group of patients, with 47% of patients improving by one class. Only 15% of patients in the historical control group improved by one class.

Cardiopulmonary haemodynamic function

We measured cardiopulmonary haemodynamic function in both the historical control group and the current treatment era group. Those patients with mPAP > 40 mm Hg and PVR > 600 dyn·s·cm^{-5} had worse long term outcomes. PVR increased during follow up in the historical control patients but did not increase in the current treatment era group. This suggests that high pulmonary artery pressures identify patients at high risk who have a poor prognosis and that reduction in PVR and mPAP are important influences on survival. Therefore, the improved survival in the current treatment era group of patients may be due to improved or lack of deterioration of haemodynamic function, reducing right heart work with consequent improvements in right heart failure. In view of the progressive deterioration in haemodynamic function in our historical control group, the haemodynamic follow-up data in the current treatment era patients probably indicated stabilisation of their haemodynamic function rather than merely a lack of pharmacological effect.

Limitations of the study

Because this was not a randomised controlled study and some of the patients treated in the current treatment era received both bosentan and a prostanoid, it is not possible to attribute this improvement to any specific therapeutic agent but rather to a more aggressive treatment approach. This has involved earlier treatment, with more intensive dose regimens and more use of combination drugs.

As this was an open label study, the WHO class improvements may have been partially due to a placebo effect; however, non-subjective parameters such as the improved survival and cardiac haemodynamic function cannot be explained by a placebo effect.

End stage patients were excluded from this study, as in the recent treatment trials. Thus, the conclusions cannot be applied to end stage patients.

None of our patients received sildenafil, as no published data support treatment with phosphodiesterase during the period under analysis. Further work is now required to establish the place of sildenafil and other phosphodiesterases in the treatment of SSc-PAH.

Conclusion

We believe this is the first trial to document an improvement in survival with SSc-PAH. In the absence of properly conducted randomised trials, the data presented support bosentan as a reasonable preferred treatment approach for moderately severe SSc-PAH. When backed by early high dose prostanoid treatment in patients who do not respond, preferred treatment with bosentan is associated with improved survival, well-being and haemodynamic function.

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